Renal artery stenosis: A cardiovascular perspective
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Background Renal artery stenosis (RAS) is an important clinical entity that can lead to uncontrolled hypertension and progressive renal failure. The most common causes of RAS are atherosclerosis and fibromuscular dysplasia. Because the diagnosis of renovascular hypertension is established only when revascularization of a stenosed renal artery results in cure or improvement in patients hypertension, establishment of a causal relationship between RAS and hypertension continues to present a challenge. Therefore, a high index of suspicion is essential in the diagnosis of this condition.

Methods Multiple tests, both invasive and noninvasive, are available as screening methods. Angiography remains the gold standard for diagnosis of RAS. Besides its value in establishing the diagnosis, it provides anatomic information regarding the site and severity of stenoses and appropriate revascularization strategies. Magnetic resonance angiography and duplex ultrasonography are the most promising and accurate noninvasive screening tests available, even in the presence of renal insufficiency. With advances in percutaneous transluminal angioplasty techniques, including renal artery stenting, many more patients are eligible for less invasive and effective revascularization strategies compared with the traditional surgical procedures.

Results Revascularization of a stenosed renal artery is associated with preservation of renal function and better control of hypertension, unstable angina, and congestive heart failure. Because atherosclerotic RAS is associated with generalized atherosclerosis, aggressive risk factor modification and antiplatelet therapy are integral in the management of RAS regardless of the revascularization strategy. [Am Heart J 2002;143:559-64.]

Renal artery stenosis (RAS) is a frequently overlooked clinical entity that can cause uncontrolled hypertension and can lead to a progressive deterioration of renal function.1-5 Table I shows the different causes of RAS. The 2 major types are atherosclerosis and fibromuscular dysplasia. Fibromuscular dysplasia is a rare entity that can cause secondary hypertension. Revascularization can lead to cure of hypertension or a significant improvement in blood pressure control in most affected patients. On the contrary, atherosclerotic RAS is a common disease particularly in association with the presence of atherosclerosis elsewhere.6-10

Distinguishing between RAS and renovascular hypertension is important because the former does not always result in hypertension or hypertension may not be related to RAS. In this review, we will focus on the 2 major types of RAS and will discuss the pathophysiology, clinical presentation, diagnostic methods, and management strategies.

Pathophysiology
Unilateral RAS with 2 functional kidneys leads to increased renin secretion by the affected kidney and suppression of its secretion by the contralateral kidney. Renin moderates the conversion of angiotensinogen to angiotensin I, which then converts to angiotensin II with the angiotensin-converting enzyme (ACE). Angiotensin II causes vasoconstriction, which leads to hypertension and enhances the adrenal synthesis of aldosterone. Aldosterone causes sodium and fluid retention, which also promote the development of hypertension. With sodium retention, volume expansion, and hypertension, the contralateral kidney responds with diuresis leading to sodium and water excretion to restore plasma volume to normal. Early revascularization will cure hypertension in these patients. However, damage to the healthy kidney from sustained hypertension may limit the benefit of revascularization if performed too late.11

In bilateral RAS (or RAS of a solitary kidney), renin secretion is increased by both kidneys. Subsequently, plasma volume expands rapidly because of the lack of a healthy kidney that can initiate diuresis. With plasma volume expansion, renin secretion will ultimately decrease. Besides renin, sympathetic nervous system,12 nitric oxide, and others are implicated in the development of renovascular hypertension and are currently under investigation. Nitric oxide produces cyclic guanosine monophosphate–dependent smooth muscle cell...
Causes of renal artery stenosis

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<th>Condition</th>
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<td>Atherosclerosis</td>
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<td>Fibromuscular dysplasia</td>
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<td>Aortic or renal artery dissection</td>
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<td>Nonspecific aortoarteritis (Takayasu’s arteritis)</td>
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<td>Posttransplantation stenosis</td>
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Table 1. Causes of renal artery stenosis

Relaxation and is an important regulator of renal homeostasis and vascular hemodynamics. Several animal studies showed that inhibition of nitric oxide synthesis increased vascular tone that resulted in hypertension and renal dysfunction.

Clinical features suggestive of renal artery stenosis

A high index of clinical suspicion is paramount in the diagnosis of RAS. Patients with general hypertension have a low prevalence of renovascular hypertension. Thus, it is not cost-effective to screen all patients with hypertension for RAS. A careful review of medical history and thorough physical examination should be performed in all patients with hypertension to recognize important features suggestive of renovascular hypertension. Because the diagnosis of renovascular hypertension is only established when revascularization of a stenosed renal artery results in cure or improvement of patient blood pressure control, screening should be reserved for those patients with 1 or more clues suggestive of renovascular hypertension as: 1, onset of hypertension before age 30 years or after 55 years; 2, malignant or accelerated hypertension; 3, sudden onset of uncontrolled hypertension that was previously well controlled; 4, evidence of diffuse atherosclerosis; 5, epigastric bruit, particularly during diastole; 6, azotemia induced by ACE inhibitor; 7, unexplained azotemia; 8, a unilateral small kidney; and 9, flash pulmonary edema in the presence of hypertension and normal left ventricular function.

Diagnostic methods

Numerous invasive and noninvasive tests are available to screen for RAS in appropriate patients. Several methods should no longer be practiced. Intravenous urography is no longer used because of poor sensitivity and specificity. Measurement of plasma renin activity is influenced by multiple medications and also has a poor sensitivity and specificity. The results of plasma renin activity can be improved after a single dose of captopril. However, it lacks anatomic information regarding the renal arteries, kidney involvement, or function. Moreover, antihypertensive medications have to be discontinued several days before testing, and the results are not accurate in patients with renal insufficiency. Several other noninvasive screening tests are available that provide better screening for RAS. The following methods are used widely and offer various levels of benefit.

Doppler ultrasonography. This procedure provides an assessment of the kidney size and structure and a functional evaluation of the renal arteries and severity of stenosis. Sensitivity and specificity are usually operator dependent and usually exceed 90% in dedicated laboratories. The test is noninvasive and safe in all age groups and in patients with impaired renal function. It is also useful for serial follow-up examination after revascularization.

Captopril renography. Captopril renography is a highly sensitive and specific nuclear imaging test that can be used to identify critical RAS. However, the test lacks anatomic information about the renal arteries, and its accuracy is reduced in patients with impaired renal function. The test consists of renal imaging with markers of glomerular filtration rate (GFR), such as technetium-99m diethylenetriamine penta-acetic acid, 99mTc-mercaptodiglycine, and iodine-131 orthiodohippurate. Tracer is given at baseline and again 30 to 60 minutes after ingestion of 25 to 50 mg of captopril. The test is considered suggestive of RAS when there is a delayed peak uptake of the tracer for more than 10 minutes (normal, 3 to 6 minutes) in the affected kidney or a decreased relative uptake in the affected kidney reflecting less than 40% of GFR. The wash out of isotope in the affected kidney may be delayed as compared with the unaffected side. The sensitivity and specificity of captopril renal scan for predicting cure after revascularization are 100% and 50%, respectively.

Magnetic resonance angiography. With its improved software and digital subtraction techniques, the sensitivity and specificity of this test to diagnose RAS exceeds 90%. It is entirely a noninvasive technique and has no specific contraindications. Major disadvantages are related to costs, and false-positive artifacts are related to respiration, peristalsis, and tortuous vessels. Other limitations are related to inability to identify nonostial stenosis or stenoses in accessory renal arteries.

Spiral computed tomography with angiography. This procedure combines high sensitivity and specificity. However, the need for contrast and its related complications limits its usefulness in patients with impaired renal function.

Renal angiography. Renal angiography remains the gold standard for diagnosis; it provides information about the site and severity of stenoses and appropriate revascularization strategies. Digital subtraction technique allows utilization of less contrast material resulting in a lower risk of contrast-induced nephrotoxicity.
in patients with advanced renal insufficiency. The use of carbon dioxide or gadolinium as contrast agents avoids the risk of contrast-induced nephrotoxicity.

**Recommended approach**

For patients with low likelihood of RAS, such as most patients with hypertension, specific testing to evaluate RAS is not recommended. For those patients who have clinical features of RAS and need angiography for other reasons (coronary or peripheral angiography), abdominal aortic angiography with or without selective renal angiography during the same procedure to identify the renal vasculature is safe and should be the procedure of choice for diagnosing RAS. On the other hand, for patients who do not need other angiography, screening should start with noninvasive testing. The choice of noninvasive method depends on the availability and familiarity of the treating physician with various tests. Occasionally, multiple tests are necessary and complimentary for accurate diagnosis. For those patients in whom noninvasive tests are not diagnostic and those who are considered for renal artery revascularization, arteriography should be considered. Figure 1 outlines the diagnostic approach for patients suspected of having RAS.

**Management**

The management of patients with RAS is controversial, particularly in regards to the timing and strategy of revascularization. However, general guidelines of the different management methods will be addressed in this review. In general, a stenosis becomes hemodynamically significant when it occludes 70% or more of the renal artery diameter. Because the presence of stenosis in patients with hypertension does not mean renovascular hypertension, revascularization should be considered in a select group of patients suspected of having renovascular hypertension with significant stenosis. Revascularization of these patients is associated with preservation of renal function and better control of hypertension, unstable angina, and congestive heart failure. Because of improvement in percutaneous revascularization techniques, more patients with RAS are becoming amenable to less invasive procedures, such as renal angioplasty with or without stenting.

**Percutaneous revascularization.** Percutaneous transluminal renal angioplasty (PTRA) is currently the treatment of choice for patients with fibromuscular dysplasia. Stenting is usually not necessary, and recurrence rates are low, approximately 5%. Successful PTRA in these patients is expected to result in cure of hypertension or significant improvement in blood pressure control, and loss of renal function is uncommon.

Atherosclerotic RAS is usually seen in elderly patients with evidence of generalized atherosclerosis including the aorta. The lesion usually involves the proximal renal artery, particularly the ostium, and extends into the aorta. Angioplasty in this group of patients is usually limited by recoil and high rates of restenosis that could limit the clinical benefit of revascularization. In a recently published trial, the initial modest benefit of PTRA compared with medical therapy was lost with further follow-up examination at 1 year. The most likely explanation of loss of benefits is restenosis, which approached 50% in the angioplasty group. Other possible causes of lack of benefits are related to intrinsic damage to the kidney as a result of long-standing hypertension and revascularization performed too late to benefit these patients.

On the contrary, stenting of atherosclerotic renal arteries has a high rate of procedural success and a low rate of restenosis. Renal artery stenting has been associated with better control of hypertension and preservation of renal function and is currently the procedure of choice for patients with atherosclerotic RAS that requires revascularization. The association of renal artery stenting and better control of hypertension is mainly related to maintained patency of the stented renal artery. A recent nonrandomized study showed that stenting is the appropriate therapy in patients with difficult lesions, including ostial and restenotic lesions. Results after stent placement showed superior hemodynamic and angiographic outcomes when compared with balloon angioplasty alone, and the 6-month restenosis rate was 18.8%. Similarly, other studies have shown a low rate of restenosis after renal artery stenting. Renal artery stent placement benefits on blood pressure control had no
adverse effects on renal function in patients with baseline normal or mildly impaired renal function, and the benefits were maintained up to 4 years after revascularization. Although other mechanisms may play a role in controlling blood pressure after renal artery stenting, improving blood supply to the ischemic kidney was the main mechanism.

Although these data suggest superiority of stenting compared with angioplasty in the treatment of RAS, well-designed randomized studies are not available. Thus, a randomized study to address this issue is necessary. The study should examine the long-term effects of different revascularization strategies on blood pressure control, renal function, cardiovascular morbidity, and restenosis. An evaluation of cost analysis is helpful in an environment characterized by concern about cost-effectiveness of treatments. Figure 2 shows an example of bilateral RAS before and after stenting.

**Surgical revascularization.** Surgical revascularization is currently reserved for those patients with occluded renal artery and functional but ischemic kidneys that are supplied via collateral blood flow or those associated with aortic aneurysm that require repair at the same time. It carries a mortality rate between 3% and 6%, which is usually higher in patients with other comorbid conditions, particularly cardiac and cerebrovascular diseases.

Many different procedures have evolved over the years, including atherectomy and bypass surgery, with aortorenal bypass being the most common form of anastomosis. Other anastomoses, including ileorenal, mesenterorenal, splenorenal, and hepatorenal bypass, have become more common because they involve less manipulation of the already heavily atherosclerotic aorta and thus minimize the chances of distal atheroembolism.

**Medical therapy.** In patients with atherosclerotic RAS, medical therapy is an important part of the man-
management process. Although revascularization provides a better control of hypertension, most patients will continue to use antihypertensive medications, although at lower doses or with fewer medications.

Aggressive risk factor modification, including lipid-lowering therapy, is mandatory in most patients with atherosclerotic RAS. Antiplatelet therapy is also essential, particularly for those who need percutaneous revascularization. For those patients with renovascular hypertension who are not candidates for renal artery revascularization, a careful utilization of antihypertensive medications is critical because blood pressure reduction in these patients may have significant hemodynamic effects that result in renal hypoperfusion and subsequently ischemic damage of the affected kidney. ACE inhibitors and angiotensin II receptor antagonists alter the activated renin-angiotensin system related to RAS. Thus, a careful titration of these medications to control the elevated blood pressure is an acceptable therapy as long as the deterioration of kidney function is avoided. Minor increase in serum creatinine level and a small decline in GFR is not a contraindication to these medications in this setting. In the absence of universally acceptable criteria, the magnitude of renal function changes to discontinue ACE inhibitors and angiotensin II receptor antagonists should be left to the treating physician. However, we consider an increase in serum creatinine level of 0.5 mg/dL or more or a decrease in GFR of more than 10% of the baseline value severe enough to discontinue these medications.

Patients with bilateral RAS or with stenosed renal artery in a solitary kidney are unlikely to tolerate this therapy without renal function deterioration. Thus, every effort should be exercised to revascularize this group of patients. Therefore, for most patients with unilateral RAS and 2 functional kidneys, ACE inhibitors and angiotensin II receptor antagonists are well tolerated and their use is not contraindicated as long as renal function remains stable. On the other hand, ACE inhibitors and angiotensin II receptor antagonists should be left to the treating physician. However, we consider an increase in serum creatinine level of 0.5 mg/dL or more or a decrease in GFR of more than 10% of the baseline value severe enough to discontinue these medications.

Other drugs, including diuretics and dihydropyridine calcium channel blockers, are proven to be effective in decreasing the elevated blood pressure. However, the effects of calcium channel blockers on renal function are concerning. In the African American Study of Kidney Disease and Hypertension study, ramipril offered a greater benefit in slowing renal deterioration than did amlodipine in patients with mild-to-moderate chronic renal insufficiency and proteinuria. However, amlodipine and ramipril were equally effective in patients without proteinuria.

References


